

Effect of Pre-Stroke Use of ACE Inhibitors On Ischemic Stroke Severity

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Abstract

Background: Recent trials suggest that ACE inhibitors (ACEI) are effective in prevention of ischemic stroke, as measured by reduced stroke incidence. We aimed to compare stroke severity between stroke patients who were taking ACEI before their stroke onset and those who were not, to examine the effects of pretreatment with ACE-inhibitors on ischemic stroke severity.

Methods: We studied 110 consecutive patients presenting within 24 hours of ischemic stroke onset, confirmed by DWI and PWI MRI. We calculated the NIHSS score at presentation, as the primary measure of clinical stroke severity, and categorized stroke severity as mild (NIHSS ≤ 7), moderate or severe (NIHSS ≥ 14). We measured the volumes of admission DWI and PWI lesions as a secondary measure of ischemic tissue volume. We analyzed demographic data, risk-factor profile, blood pressure (BP) and medications on admissions, and determined stroke mechanism according to TOAST criteria. We compared these variables among patients on ACE-inhibitors and those who were not. **Results:** Thirty patients (27.27 %) were on ACE-inhibitors. The baseline NIHSS score was significantly lower among ACE-treated patients (7.8 ± 6.4) than among non-ACE patients (11.1 ± 8.5 ; $p=0.04$). A significantly lower percentage of severe strokes was seen among non-ACE users (17.2% vs. 36.6%). Patients on ACE-inhibitors prior to had more milder strokes, and smaller DWI and PWI lesions volumes compared to non-ACEI treated patients. However, none of these trends were significant. There was no difference in age, time-to-imaging, risk- factor profile, concomitant therapy with lipid lowering, other antihypertensives or antithrombotic agents, or admission BP between the two groups. **Conclusions:** In this cohort of

patients pre-stroke use of ACE-inhibitors is associated with milder strokes. These results suggest that ACE-inhibitors may reduce clinical severity of stroke, as measured by NIHSS score. Further, larger-scale, studies are needed to validate our findings, and to elucidate the mechanism(s) of ACEI-mediated benefits in patients with ischemic stroke.

Background

Data from the heart outcomes prevention evaluation study (HOPE) suggest that angiotensin-converting enzyme inhibitors (ACEI) are effective in prevention of ischemic stroke, as measured by reduced stroke incidence in subjects randomized to treatment with ACEI [1]. In this trial, the use of the ACEI, ramipril, resulted in a 32% reduction in ischemic stroke risk despite minimal reduction in blood pressure (BP) [1]. This reduction in stroke rate is 3 times the decrease that would be expected if ramipril's effects were based on its BP lowering properties alone, since the mean reduction in BP with treatment was only 3/2 mmHg. This discrepancy suggests that ACEI may exert direct, BP-independent, neuroprotective effects.

To further elucidate if ACEI have potential neuroprotective effects, we tested whether their use prior to ischemic stroke onset might also reduce the severity of stroke. We examined clinical and admission magnetic resonance imaging (MRI) data from patients with ischemic stroke to determine the effects of pre-stroke use of ACEI on stroke severity.

Methods

Study Design and Patient Selection

We retrospectively reviewed our prospectively collected stroke database. We identified consecutive patients (over a time period of 30 months) presenting with ischemic stroke within 24 hours of stroke onset, as confirmed by diffusion- and perfusion-weighted MRI (DWI/PWI) upon admission. We included all patients who had interpretable diffusion- and perfusion-weighted images, including those who had received thrombolytic, endovascular or experimental neuroprotective treatment. We only excluded patients who did not undergo DWI/PWI, and patients in whom the MRI images were of poor quality to allow adequate quantitative analysis.

Data Collection and Assessments

We retrieved the following data for each patient: (1) demographics; (2) risk factors for stroke, i.e. hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, coronary artery disease (CAD), atrial fibrillation (AF), congestive heart failure (CHF) and smoking, as reported by the patient and his/her family; (3) vital signs at presentation (BP and temperature); (4) blood glucose level at admission; (5) medications upon admission, with particular attention to antiplatelets, anticoagulants, lipid-lowering agents, and antihypertensives including ACEI. We did not collect information about the dose or duration of medication(s) use; (6) the baseline National Institute of Health Stroke Scale (NIHSS) score [2], which was recorded by stroke-trained

Neurologists certified in the application of NIHSS at admission; and (7) time from stroke-detection to imaging.

Outcome measures

We used the NIHSS score at presentation as the primary measure of clinical stroke severity, and categorized stroke severity as mild (NIHSS score < 7), moderate (NIHSS score 7-14) or severe (NIHSS score > 14). We measured the total DWI and PWI lesion volumes, as secondary radiological measures of stroke severity. All MRI studies were performed on a Siemens Medical Systems Vision 1.5-T MR whole body scanner with echoplanar imaging capabilities. The volume of the perfusion abnormality was measured on relative Mean Transit Time (rMTT) maps. The specific MRI sequence parameters, imaging processing and volumetric analysis are described in details in previous publications [3-4]. We classified stroke mechanisms, after completing the diagnostic work-up, according to the Trial of Org 10172 in Acute Treatment (TOAST) criteria [5].

Statistical Analysis

We divided patients into 2 groups; those who were taking ACEI before their stroke onset and those who were not. We compared inter-group differences between individual categorical variables by using Fisher's exact test and Wilcoxon rank sum test for continuous variables, as appropriate. To assess the role of possible confounding variables, such as age, sex and risk factor profile, we compared various characteristics between the 2 groups using adjusted Cochran-Mantel-Haenszel mean score rank test. A *p*-value of < 0.05 was considered statistically significant for all analyses.

Results

Patient Characteristics (Demographic and Clinical Features)

A total of 126 patients were identified. Of these, only 110 met all of our inclusion and none of the exclusion criteria, and were included in subsequent analyses. Approximately, 27% (30 of 110 patients) were on ACEI before stroke onset. Table 1 summarizes the demographic and clinical features of patients in both ACEI- and non ACEI-treated groups. There were no significant differences in the mean age or sex distribution between the 2 groups. Predictably, there was a trend for a higher frequency of hypertension, hyperlipidemia and cardiac disease, in particular CHF, in the ACEI-treated group. However, only hypertension (80% vs. 57%; $p = 0.03$, Fisher test) and CHF (19% vs. 7%; $p = 0.027$, Fisher test), were statistically different in both groups. Other risk factors, such as smoking, DM, AF and CAD were not statistically different.

A slightly lower percentage of patients in the ACEI-treated group were imaged within 6 hours from stroke onset, compared to the non ACEI-treated group (59% vs. 66%). However, this difference was not statistically significant. There were no significant differences in admission temperature or glucose levels between the 2 groups. The mean SBP upon admission was 159 ± 29 mmHg in ACEI-treated patients vs. 153 ± 26 mmHg in non-ACEI group, and the mean DBP was 81 ± 15 vs. 78 ± 15 mmHg. None of these differences were statistically significant.

The vast majority of patients who were using ACEI at the time of stroke onset were taking enalapril (n = 13) or lisinopril (n = 12); 4 patients were taking captopril and 1 accupril. None of our patients was taking perindopril or ramipril, or a combination of different ACEI. A roughly equal percentage of patients in each group were using antiplatelets, anticoagulants, statins and other BP lowering agents. Similarly, the frequency of using other classes of antihypertensive agents was not significantly different in either group. Three patients were taking angiotensin receptor blockers (ARBs) at the time of their stroke. None of these 3 patients was on ACEI. They were all included in non ACEI-treated group for purposes of statistical analysis.

Patient Outcomes

The mean NIHSS score at admission was significantly lower in ACEI-treated patients (7.8 ± 6.5 vs. 11.1 ± 7.9 ; $p = 0.042$, Wilcoxon rank sum test). This difference remained statistically significant after controlling for possible confounding variables, such as history of hypertension, hyperlipidemia and cardiac disease, including CHF, using the Cochran-Mantel-Haenszel row mean score test using ranks adjusted for these factors ($p = 0.044$).

Figure 1 depicts the categorization of NIHSS scores according to severity. As it shows, ACEI-treated patients had more mild and moderate strokes than their non ACEI-treated counterparts. However, these trends were not statistically significant. A significantly lower percentage of patients in the ACEI-treated group had severe strokes, defined as NIHSS score > 14 , compared with non ACEI-treated patients (17% vs. 37%; $p = 0.037$, Fisher test).

Figure 2 shows the distribution of stroke mechanisms, according to TOAST criteria, among ACEI- and non ACEI-treated patients. The stroke mechanisms were roughly equivalent in both groups. Although, cardioembolic cause was more frequent among non ACEI-treated patients (29% vs. 22%) and lacunar etiology was more commonly seen among patients who were taking ACEI prior to stroke onset (25% vs. 17%), these differences were not statistically significant.

There were no significant differences between both groups with regard to the mean diffusion, perfusion or perfusion-diffusion (mismatch) lesion volumes (Table 2).

Discussion

We found that the baseline NIHSS score was lower in patients who were taking ACEI prior to their stroke compared to those who were not taking ACEI at the time of stroke onset. The NIHSS is accepted widely for measuring acute stroke deficits to assess the degree of severity of neurological deficits from stroke and its reliability has been tested in several clinical trials [6-8].

We found no difference in admission BP between ACEI and non-ACEI users, suggesting that the beneficial effects of ACEI use may not be directly related to their BP-lowering effect. This is concordant with the results from the HOPE trial [1].

Our findings are unlikely to be related to differences in baseline risk factor profile between the ACEI- and non-ACEI treated patients. Patients who were

on ACEI had a higher prevalence of hypertension and heart failure, which may have biased our data toward higher stroke severity in ACEI-treated patients, and thus limited our ability to detect larger differences in favour of ACEI use. Since the observed beneficial effect of ACEI on stroke severity could potentially be secondary to ACEI effects on stroke mechanism, we examined the impact of ACEI use on stroke mechanism using TOAST criteria. ACEI use did not seem to influence stroke mechanism in our cohort of patients, since the difference(s) in stroke cause/type were not statistically different between ACEI- and non ACEI-treated patients. Similarly, the beneficial effect of ACEI in our patients is unlikely to be related to other concomitant treatments. Although, several patients in both groups were on statins, antithrombotics and other antihypertensive agents, we found no significant difference between ACEI- and non ACEI-treated patients receiving any of these classes of drugs.

A recent prospective observational study of 507 patients with first-ever ischemic stroke showed that treatment with ACEI at the time of stroke onset is associated with reduced plasma concentration of C-reactive protein and better long-term outcomes [9], suggesting that ACEI may have anti-inflammatory properties and reduce the acute-phase inflammatory response after stroke onset. There are several other potential mechanisms by which ACEI may provide benefit to stroke patients. Experimental data suggest that the rennin-angiotensin system modulates the atherosclerotic process, and that angiotensin II exerts pro-inflammatory actions in the vascular wall, which induce the production of reactive oxygen species and hydroxyl radicals,

cytokines and adhesion molecules [10-15]. Angiotensin converting enzyme inhibitors could provide neuroprotection via blockade of angiotensin II-mediated endothelial dysfunction, lipid peroxidation and subsequent oxidative stress, and vascular smooth muscle intracellular calcium accumulation and hypertrophy [10-16]. Furthermore, ACEI may help maintain homeostatic balance of fibrinolytic and procoagulant factors [17] and increase cerebral blood flow [18].

We found that ACE I use had no effect on MRI measures of ischemic lesion volume. This discrepancy between the beneficial effects of ACEI on clinical, but not radiological, measures of stroke severity is reconcilable since the correlation between infarct volume and NIHSS is only moderate, particularly in non-dominant hemispheric strokes [19-21]. We explored the possibility that the lower NIHSS scores in ACEI-treated patients might be secondary to a higher percentage of non-dominant hemispheric strokes in this group [21]. However, we found no significant difference in the preponderance of non-dominant hemispheric strokes between the 2 groups (data not reported). Infarct location, not only size, is also an important determinant of the severity of clinical deficits and our small sample size may have limited our ability to detect a difference in favour of ACEI.

We acknowledge that our study has inherent limitations imposed by its retrospective nature, non-randomization of treatment allocation and small sample size. The small number of ACEI-treated patients does not allow us to test for possible differences among the various ACEI. Most importantly, our

study lacks follow-up data regarding the effect of ACEI use on long-term outcomes since a large percentage of our patients were either enrolled in experimental neuroprotective trials or treated with thrombolysis upon presentation.

Conclusions

Our results show that pre-stroke use of ACEI is associated with milder stroke severity, as assessed by NIHSS score. Our findings need to be prospectively validated in larger-scale randomised studies, and the mechanism(s) of ACEI-mediated benefits in patients with ischemic stroke need to be elucidated.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MS designed the study, collected and analyzed data, wrote the paper, and carried out critical revision of the manuscript. SS collected and analyzed data, and reviewed the manuscript. IL collected data and reviewed the manuscript. LR critically reviewed the manuscript. GS collected data, and carried out critical revision of the manuscript.

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Figures

Figure 1 - Comparison of clinical severity of stroke between ACEI- and non ACEI-treated patients.

Figure 2 - Comparison of stroke mechanisms between ACEI- and non ACEI-treated patients.

Tables

Table 1 - Comparison of demographic and clinical features between ACEI- and non ACEI-treated groups.

	ACEI Group	Non-ACEI Group	
Number of patients	30 (27%)	80 (73%)	
Sex (women/men)	12/18	39/41	
Mean age (yr) \pm SD	72 \pm 10	67 \pm 16	
Risk Factors			
History of hypertension	80%*	57%	p = 0.03
History of diabetes	30%	26%	
History of hyperlipidemia	30%	18%	
History of cardiac disease	33%	17%	
CHF	19%*	7%	p = 0.027
AF	11%	6%	
CAD	3%	4%	
History of smoking	12%	9%	
Concomitant medications			
Antiplatelets	33%	39%	
Anticoagulants	13%	8%	
Statins	17%	16%	
Other BP lowering agents	47%	52%	
Diuretics	32%	25%	
B-blockers	39%	33%	
Ca ⁺⁺ blockers	25%	23%	
Time from stroke-to-imaging			
0-6 h	59%	66%	
6-24 h	41%	34%	
Clinical features			
NIHSS score, mean	7.8 \pm 6.5*	11.1 \pm 7.9	p = 0.04
SBP (mean \pm SD), mmHg	159 \pm 29	153 \pm 26	
DBP (mean \pm SD), mmHg	81 \pm 15	78 \pm 15	

Abbreviations: Year (yr); Standard deviation (SD); Congestive heart failure (CHF); Atrial fibrillation (AF); Coronary artery disease (CAD); Hour (h); Statistically significant, i.e. $p < 0.05$

(*).

Table 2 - Comparison of MRI between ACEI- and non ACEI-treated group

	ACEI Group	Non-ACEI Group
DWI lesion volume (mean \pm SD), cm ³	25.2 \pm 23.4	28.7 \pm 25.0
PWI lesion volume (mean \pm SD), cm ³	72.6 \pm 56.6	75.1 \pm 68.5
Mismatch (PWI – DWI) volume (mean \pm SD), cm ³	47.6 \pm 39.5	46.6 \pm 28.2

Additional files

None

Figure 1

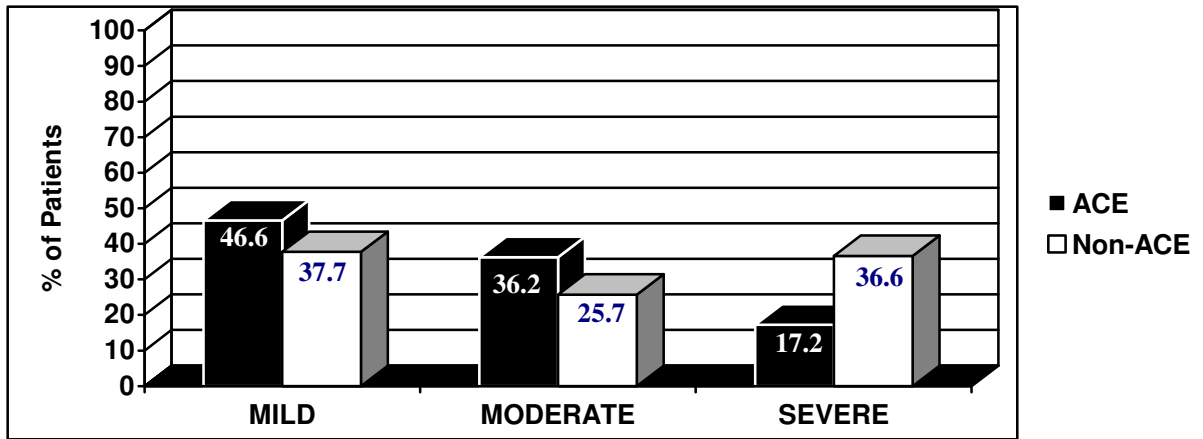


Figure 2

